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| EXAMINER | |
|---|---|
| HUANG, GIGI GEORGIANA | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1612 | |

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| 01/27/2009 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ADIPFDD@bipc.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/801,078 | PALCZEWSKI ET AL. | |
| | Examiner | Art Unit | |
| | GIGI HUANG | 1612 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *19 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *16-21,35-43,45,47 and 48* is/are pending in the application.

4a) Of the above claim(s) *47 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-21,35-43 and 45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/19/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application*

1. The response filed September 19, 2008 has been received, entered and carefully considered. The response affects the instant application accordingly:

   a. Claims 16 and 45 have been amended.

   b. Claims 22, 44, and 46 have been cancelled.

   c. Claim 47-48 has been added.

2. Claims 16-21, 35-43, 45, 47-48 are pending in the case.

3. Claims 16-21, 35-43 and 45 are present for examination.

4. The text of those sections of title 35.U.S. Code not included in this action can be found in the prior Office action.

5. All grounds not addressed in the action are withdrawn or moot.

6. New grounds of rejection are set forth in the current office action.

### *Election/Restrictions*

7. Newly submitted claim 47-48 are not directed to the elected species of 11-cis-7-ring retinal and are withdrawn from consideration as being directed to a non-elected invention.

### *New Grounds of Rejection*

8. Due to the amendment of the claims the new grounds of rejection are applied:

### *Claim Rejections - 35 USC § 112*

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claim 16-21, 35-43, and 45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method of treating a human subject with a loss of photoreceptor function expressing a mutant opsin protein with a substitution of Proline 23 by Histidine with the administration of an effective amount of an opsin-binding synthetic retinoid in a pharmaceutically acceptable vehicle. However, the specification does not present and describe an example where the synthetic retinoid was administered to a human subject suffering from a condition due to the expression of a mutant opsin protein with the substitution of Proline 23 with the Histidine for the treatment of photoreceptor function. There are cell line tests but not the administration of the retinoid to a human subject suffering the loss of photoreceptor function from the expression of a mutant opsin protein with a proline 23 substitution with histidine. Secondly, the specification does not describe any condition other than retinitis pigmentosa expressing a mutant opsin protein with a substitution of Proline 23 with Histidine. As a result, the fact pattern indicates that the only condition Applicant is in possession of with the claimed mutant opsin protein is retinitis pigmentosa resulting from the mutation of proline23 substituted by histidine.

11. Claims 16-21, 35-43 and 45 are rejected under 35 U.S.C. 112, first paragraph, because the specification and the art, while being enabling for treatment of retinitis pigmentosa due to the expression of mutant P23H-opsin in a human suffering from the condition with 11-cis-7 ring retinoid, 11-cis retinol, and vitamin A, does not reasonably provide enablement for any other synthetic retinoid for the treatment of retinitis pigmentosa due to the expression of mutant P23H-opsin in a human suffering from the condition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

*(1) The nature of the invention and (2) the breadth of the claims:*

The claims are drawn to a method of treatment for human suffering from the condition retinitis pigmentosa due to the expression of mutant P23H-opsin with any

synthetic opsin-binding retinoid. Thus, the claims taken together with the specification imply that any synthetic opsin-binding retinoid can treat a human suffering from the condition retinitis pigmentosa due to the expression of mutant P23H-opsin.

*(3) The state of the prior art and (4) the predictability or unpredictability of the art:*

Berson (Retinitis pigmentosa: Unfolding its mystery) teaches that administration of a supplement with 15,000 IU of vitamin A daily slows the progression of retinitis pigmentosa (which includes the P23H form). Berson also teaches the unpredictability and the mystery of different forms of retinitis pigmentosa. Chatzinoff et al. teaches the use of 11-cis-isomer of vitamin A (retinal) or an ester for retinitis pigmentosa which encompasses the P23H form of the condition.

*(5) The relative skill of those in the art:*

The relative skill in those in the art is high.

*(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:*

The specification has provided guidance for the formation of pigment with 11-cis-7 ring retinoids (utilized for specific 11-cis-7-ring compounds see Figure 1b) with P23H opsin. The specification also showed that no significant pigment was seen with either 11-cis-6-ring retinal or 11-cis-9-demethyl-7-ring retinal, citing that these studies illustrated the *unique* specificity of binding between 11-cis-7-rig retinal and P23H opsin.

As a result, the art provides for vitamin A and the specification only provides support for the single retinoid 11-cis-7-ring retinoid to be effective for P23H and does not provide adequate support for the entire generic nor the specific synthetic retinoid

other than 11-cis-7-retinal claimed, as there are an insufficient amount of representative examples to anticipate the multitude of compounds claimed, as a single example does not and as cited by the specification, there are negative results for the retinoids tested with P23H mutant opsin, which goes to the specific interaction of 11-cis-7-ring retinoid and P23H-opsin and unpredictability of the art.

*(8) The quantity of experimentation necessary*:

Considering the state of the art as discussed by the references above, particularly with regards to the use for the broad genus of synthetic retinoids for the specific patient population claimed, the lack of enablement for some of the forms claimed, and the specificity present in the specification for the 11-cis-7-ring form for P23H, the presentation by the art for vitamin A and 11-cis vitamin A, and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claim 16-21, 35-43 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are unclear as to what conditions have a loss of photoreceptor function from the expression of a mutant opsin protein with a substitution of Proline 23 with Histidine. The specification only describes a specific subset pf patients with the

condition retinitis pigmentosa to present with the mutant substitution. It is unclear what other, if any conditions have the particular claimed mutant opsin protein. It is unclear if applicant is directing the claims to the broad generic condition of retinitis pigmentosa, the specific patient subset of patients with retinitis pigmentosa due to the mutant P23H, or to a different condition other than retinitis pigmentosa with the mutant proline 23 substitution with histidine. It does not allow one of skill in the art to ascertain the metes and bounds of the invention. For purposes of prosecution, the condition of a loss of photoreceptor function due to the expression of a mutant opsin protein with a substitution of Proline 23 by Histidine in a human suffering from the condition will be viewed as the specific patient population with retinitis pigmentosa due to mutant proline 23 substitution with histidine.

14. Claim 17-18, 39-40 recites the limitation "vertebrate" in claim 16. There is insufficient antecedent basis for this limitation in the claim.

***Claim Rejections - 35 USC § 102***

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

16. Claim 16-17 rejected under 35 U.S.C. 102(b) as being anticipated by Kupfer et al. (Information for Doctors Who Follow Patients with Retinitis Pigmentosa) or alternatively Berson (Retinitis pigmentosa: Unfolding its mystery) .

The National Eye Institute teaches that administration of a supplement with 15,000 IU of vitamin A daily slows the progression of retinitis pigmentosa. Berson teaches that oral vitamin A therapy is effective in the treatment of the common forms of retinitis pigmentosa which anticipates P23H as it is the most common form of the autosomal dominant retinitis pigmentosa as addressed in the specification.

***Claim Rejections - 35 USC § 103***

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 16-18 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chatzinoff et al. (U.S. Pat. No. 3196078).

Chatzinoff et al. teaches the use of 11-cis-isomer of vitamin A (retinal) or an ester for retinitis pigmentosa. Administration can be oral or parenteral forms. Several forms are exemplified and the 11-cis isomer has great value in combating retinitis pigmentosa (see full document, particularly claims) which would be obvious to one of skill in the art to utilize for all forms of retinitis pigmentosa including P23H, absent any evidence to the contrary. One would be motivated to do so as it is desirable to treat all forms of a condition with a composition taught to be useful for the general condition (see full document).

19. Claims 16-21, 35-43 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chatzinoff et al. (U.S. Pat. No. 3196078) as applied to claims 16-19, 22, 44-46 above, in view of Kuksa et al. (Biochemical and Physiological properties of Rhodopsin Regenerated with 11-cis-6-Ring and 7-Ring-retinals), and further in view of Klimko (U.S. Pat. No. 6300328).

Chatzinoff et al. teaches the use of 11-cis-isomer of vitamin A (retinal) or an ester for retinitis pigmentosa. Administration can be oral or parenteral forms. Several forms are exemplified and the 11-cis isomer has great value in combating retinitis pigmentosa (see full document, particularly claims) which would apply to any form or retinitis pigmentosa including P23H (see full document).

Chatzinoff et al. does not expressly teach the incorporation of a 11-cis-7-Ring neither retinal nor local administration of retinals.

Kuksa et al. teaches the biochemical and physiological effect of retinal analogs with different ring sizes that prevented isomerization around the C11 and C12 double bond. Kuksa taught that the 11-cis-7-ring did not isomerizes along the double bonds and appears to bind tightly with the opsin as it mimics the structure of 11-cis-retinal. Among the 11-cis-7 retinal isomers modeled is cycloheptatrienylidene 11-cis-locked retinal (see Figure 1, A, 3). Kuksa teaches that the constrained retinoids particularly the 11-cis-7 retinal has potential use to activate opsin in some retinal degeneration diseases. The 11-cis-7 ring form readily bound to opsin in vivo and formed stable pigment which was the most sable isomer (isomer 3). Specifically mentioned are

conditions such as Leber congenital amaurosis (LCA) and autosomal recessive retinitis pigmentosa (see full document).

Klimko teaches pharmaceutical forms for methods of administration that are known in the art for ophthalmic conditions (e.g. retinitis pigmentosa) including oral administration (e.g. tablets, capsules, solutions), parenteral use (e.g. solutions and suspensions), topical administration (e.g. solutions, suspensions, eye drops), and intraocular (includes retrobulbar or periocular injections or perfusion) or depot administration (Col. 6, lines 36, 45-55, 64-68, Col.7, lines 1, 23-26, 38-43).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize the11-cis-7 ring retinal, particularly the one exemplified or modeled for LCA or autosomal recessive retinitis pigmentosa (both protein conformational disorders), as suggested by Kuksa, and produce the instant invention. It is obvious to try and utilize a 11-cis-7 retinal, particularly one modeled and known in the art, for any form of retinitis pigmentosa including P23H absent any evidence that treatment for one form would not be successful for another form of retinitis pigmentosa as Kuksa teaches that administration of these analogs have the potential to restore vision and maintaining useful vision.

One of ordinary skill in the art would have been motivated to do this because incorporation of compounds for improved and directed treatment of progressive blinding conditions is desirable.

It also would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to utilize any one of the known methods and forms of administration known in the art, as suggested by Klimko, and produce the instant invention. It is obvious to utilize any method or mode of administration known in the art, depending on the effectiveness of the compound, degree of toxicity, target area, optimal dosage levels, condition to be treated, and therapeutic profile desired.

One of ordinary skill in the art would have been motivated to do this because depending on the target area, dosage levels, condition to be treated, and therapeutic profile desired; different forms and methods of administration would be desired.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

***Response to Arguments***

20. Claims 16-22 and 35-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

Claims 22 and 44 are cancelled, the rejection is moot.

Applicant's arguments filed September 19, 2008 have been fully considered but they are not persuasive for the broad claims but are persuasive for the specific claims. Applicant asserts that the methods of screening compounds within the class of the class of compounds opsin-binding and stabilization demonstrates that the compounds possess the desired properties. This is not persuasive as there is no restriction on what compounds are used for the screening process and there is no description as to the amount or degree of binding desired, to which mutant opsin protein, as the art still in the process of finding and developing the mechanisms and gene mutations, and the purpose of screening compounds is to find compounds that are going to bind the specific desired mutant protein of P23H at an unknown degree with an unspecified amount of stabilization which is was not known as the time of filing.

Accordingly, the rejection of claims 16-18 is maintained .

21. Chatzinoff et al. (U.S. Pat. No. 3196078) in view of Kuksa et al. (Biochemical and Physiological properties of Rhodopsin Regenerated with 11-cis-6-Ring and 7-Ring-retinals), and further in view of Klimko (U.S. Pat. No. 6300328).

Applicant's arguments filed September 19, 2008 have been fully considered but they are not persuasive. Applicant's argument with respect to teaching away with the term "inactive" is not persuasive as it is an obvious typographical error base on the art and has been corrected in the rejection above. Applicant's argument with respect to the negative teaching are not persuasive as the 11-cis vitamin A is administered intramuscularly and Chatzinoff teaches not only the 11-cis vitamin A form but also its esters administered orally or parenterally for which are different modes of administration

and encompass different compounds retinitis pigmentosa (which encompasses all the forms including P23H). As the study does not address the 11-cis-vitamin A in the different modes of administration or administration of the esters, it does not negate the teachings of Chatzinoff. Even if the study is a negative teaching to an intramuscular aspect of 11-cis vitamin A for Chatzinoff, it still provides a teaching that different forms of vitamin A are useful for the condition and provides and obvious reason and motivation to evaluate and use similar retinoids.

22. Claims 16-22 and 35-46 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 8-11, 59, 62, 70-104 of copending Application No. 10/548612.

Claims 22 and 44 are cancelled, the rejection is moot.

Applicant's arguments filed September 19, 2008 have been fully considered but they are not persuasive. Applicant's argument that the amendments for the expression of P23H mutant opsin moots the provisional rejection is not persuasive as the instant claims are viewed to a human suffering from retinitis pigmentosa due to mutant proline 23 substitution with histidine which anticipate the broader copending claims. However, as it is unclear what other conditions are addressed with the mutant opsin P23H (see 112 rejection) such as LCA and would also anticipate the copending claims.

***Conclusion***

23. Claims 16-21, 35-43, and 45 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GIGI HUANG whose telephone number is (571)272-9073. The examiner can normally be reached on Monday-Thursday 8:30AM-6:00PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fredrick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

GH
/Zohreh A Fay/
Primary Examiner, Art Unit 1612